UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,632	01/25/2002	Ronald M. Burch	200.1079CON7	3301

23280 7590 08/10/2006

DAVIDSON, DAVIDSON & KAPPEL, LLC
485 SEVENTH AVENUE, 14TH FLOOR
NEW YORK, NY 10018

EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 08/10/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,632	BURCH ET AL.	
	Examiner	Art Unit	
	Jon D. Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 July 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *38 and 47-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *38 and 47-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Please note: There is a change in Examiner handling prosecution in this case from Padmashri Ponnaluri to Jon D. Epperson.

Status of the Application

1. The Response filed April 11, 2006 is acknowledged.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior office action.

Status of the Claims

3. Claims 38 and 47-52 were pending. No claims were added, canceled or amended. Therefore, claims 38 and 47-52 are currently pending and examined on the merits.

Withdrawn Objections/Rejections

4. All rejections are maintained and the arguments are addressed below.

Outstanding Objections and/or Rejections

Claim Rejections - 35 USC 103

5. Claims 38, 47, 48, 50-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. US Pat. No. 4,569,937 (2/86) and Tanaka et al., Arzneimittel-Forschung (1992) Vol. 42(7) pages 935-44.

The instant claims briefly recite a method of effectively treating pain in humans comprising orally administering to a human patient an oral dosage form comprising analgesic compounds consisting essentially of (i) N-[3-formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl]methanesulfonamide and/or at least one pharmaceutically acceptable salt thereof; and (ii) oxycodone and/or at least one pharmaceutically acceptable salt thereof.

Baker et al. teach pharmaceutical compositions for relieving pain in humans comprising a combination of: a. a narcotic analgesic (preferably oxycodone: see formulations col. 4-8; patent claims), or a pharmaceutically acceptable salt thereof; and b. ibuprofen (a non-steroidal anti-inflammatory drug or NSAID: see col. 1-2), or a pharmaceutically acceptable suitable salt thereof, in a weight ratio of about 1:800 (e.g. .001:1) to 1:1 (compare to present claim 47:See col. 2) with oxycodone amounts of about 5 mgs-600mgs (compare to present claim 52).

The Baker reference teaches oral administration, which can be coadministered in a single dosage forms (e.g. see col. 3-8) or sequentially administered (e.g. col. 8-9 ; "... mice are dosed sequentially..."). The oral dosage forms include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4). The Baker et al. reference teach that dose ratios can be adjusted and that the analgesic activity of the combined oxycodone and ibuprofen activity is "unexpectedly enhanced" or synergistic i.e. the resulting activity is greater than the activity expected from the sum of the activities of the individual components, thereby permitting reduced dosages of narcotic analgesics (e.g. oxycodone) AND which diminishes adverse side effects (e.g. addiction) and toxicity which would result from the otherwise required amounts of the individual drug components resulting from high dosages of oxycodone or NSAID's such as ibuprofen. See e.g. col. 1-2; col. 3, lines 19-32. Accordingly, Baker would teach the use of therapeutic and

subtherapeutic amounts of oxycodone and/or ibuprofen in view of the additive or synergistic nature of the combinations and the desire to reduce the toxicity and/or side-effects of both agents; and as required by the doctor for his/her particular patient, including dosage optimization e.g. dosage overlapping of active ingredients. See e.g. col. 3 where dosage is modified to suit the particular patient.

Baker et al. further teach in view of the test results of analgesic activities of oxycodone and ibuprofen, it is possible to predict the range of maximum potentiating dosages for man, and utilizing the data from the present invention and the equivalent ratios in man, it is predicted that oxycodone amounts and the ratio of the oxycodone and ibuprofen for the oral dosage in man (i.e., see columns 12-13).

The Baker analgesic composition differs from that presently claimed in that it fails to teach the substitution of T-614 (N-[3-(formylamino)-4-oxo-6-phenoxy-4H-1-benzopyran-7-yl) for ibuprofen into the Baker compositions.

Tanaka et al. teach that T-614 possesses superior analgesic potency, as compared to ibuprofen, against inflammatory pain and antigen-induced arthritic pain in rats with virtually no gastrointestinal ulcerogenic action and no affect on water/sodium excretion (e.g., see Tanaka et al., Summary).

Accordingly, one of ordinary skill in the art would have been motivated to substitute T-614 for ibuprofen in the Baker reference compositions in light of the Tanaka reference teaching that ibuprofen is more analgesically potent with less side effects (e.g. as compared to ibuprofen) in animal models. Additionally, it is noted that the instant situation is amenable to the type of analysis set forth in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that

it is *prima facie* obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose. Thus, it would have been prima facie obvious to one of ordinary skill in the art at the time of applicant's invention to modify the Baker reference analgesic composition by substituting T-614 for ibuprofen in light of the benefits of T-614 (increased potency/decreased side effect as compared to ibuprofen) as taught by the Tanaka reference.

Response

6. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

[1] Applicants note that the presently claimed invention is restricted to analgesic compounds "consisting essentially of" the compounds set forth in claim 38 (e.g., see 4/11/06 Response, page 4, paragraph 3).

[2] Applicants argue again that the Baker reference is limited only to the use of narcotic analgesics and ibuprofen as a result of the "unexpected" synergistic activity reporter therein (e.g., see 4/11/06 Response, pages 4 and 5, especially page 5, paragraph 1). Applicants further argue that any mention of the broader class of NSAIDs cited in the Baker reference (e.g., columns 1-2, especially column 1, lines 21-32) should be ignored because these teachings appear in the

"Background" section and not in the "Experimental" and/or "Results" sections of the reference (e.g., see 4/11/06 Response, page 5, paragraph 1).

[3] Applicants again argue that the purported substitution (i.e., T-614 for ibuprofen) would change the "principle of operation" and cite MPEP 8th edition, Revision 2, p.2100-132 in support of this position (e.g., see 4/11/06 Response, page 6, paragraph 1). Applicants then subsequently conclude that the Baker et al. reference actually "teaches away" from the claimed invention because substituting ibuprofen with another NSAID would not necessarily produce the unexpected results shown for ibuprofen (e.g., see 4/11/06 Response, page 6, paragraph 2).

[4] Applicants argue again that the Examiner is improperly "picking and choosing" the methansulfonamide of the Tanaka reference with the oxycodone of Baker et al. to recreate the claims of the present invention and cite *SmithKline Diagnostics, Inc. v. Helena Laboratories* Corporation in support of this position (e.g., see 4/11/06 Response, page 6, last full paragraph).

[5] Applicants argue that the Examiner has not considered the Baker et al. reference as a whole for the reasons argued above (e.g., see 4/11/06 Response, page 7, paragraph 1).

This is not found persuasive for the following reasons:

[1] Applicant's arguments fail to comply with 37 CFR 1.111(b) because they amount to a general allegation that the claims define a patentable invention without specifically pointing out how the language of the claims patentably distinguishes them from the references. Here, Applicants note that their claims contain "consisting essentially of" language but fail to specifically point out how this limitation can be used to further distinguish the claimed invention from the prior art.

[2] The Examiner is unaware of any *per se* rule that necessarily limits the teachings of a reference to its preferred "synergistic" embodiments or teachings to certain locations within the document itself (e.g., the experimental results). To the contrary, a reference is good for all that it teaches to one of ordinary skill in the art, *In re Fritch*, 972 F.2d 1260, 1264, 23 USPQ2d 1780, 1782 (Fed. Cir. 1992), and is not limited to the particular invention described and to be protected by the patent, *EWP Corp. v. Reliance Universal Inc.*, 755 F.2d 898, 907, 225 USPQ 20, 25, (Fed. Cir.1985), the specific examples disclosed, *In re Fracalossi*, 681 F.2d 792, 794 n.1, 215 USPQ 569, 570 n.1 (CCPA 1982); *In re Lamberti*, 545 F.2d 747, 750, 192 USPQ 278, 280 (CCPA 1976), or preferred embodiments. *In re Mills*, 470 F.2d 649, 651, 176 USPQ 196, 198 (CCPA 1972). Here, Baker et al. clearly teach the use of a general class of "analgesic combinations" to relieve pain and reduce side effects that would otherwise be required by administration of the analgesic alone (e.g., see Baker et al., column 1, lines 12-17, "More active analgesic combinations are in constant demand because they offer the attractive possibility of relieving pain with reduced dosages thereby diminishing the expected side effects and toxicity that would result from the otherwise required higher dosages"). The fact that Baker et al. classifies their results as "unexpected" only serves to support this conclusion. That is, Baker et al. must have been adequately motivated to combine these analgesics "before" they realized the synergistic value of the combination (otherwise the result would not have been "unexpected" as purported). This is further supported by the express language of the patent wherein Baker et al. state, "[a] continuing goal is to be able to reduce the dosage of such narcotic analgesics by combining the m with non-addicting ingredients while still maintaining a high level of analgesia [i.e., whether the compounds exhibit a synergistic effect or not]" (e.g., see Baker et al., column 2, lines 5-8; see

also more generally column 1 and 2 disclosing several examples of analgesic combinations including various NSAIDs including combinations that do not possess a synergistic effect; see especially column 1, lines 36-37, "there is no suggestion that the combination had a synergistic effect; see also lines 27-29, "Sunshine provides no evidence or suggestions of other than an additive analgesic effect for the combinations").

[3] "A reference may be said to teach away when a person of ordinary skill, upon [examining] the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." Para-Ordnance Mfg. v. SGS Importers Int'l, 73 F.3d 1085, 1090, 37 USPQ2d 1237, 1241 (Fed. Cir. 1995) (quoting In re Gurley, 27 F.3d 551, 553, 31 USPQ2d 1130, 1131 (Fed. Cir. 1994)). The Baker et al. reference does not warn the artisan against using other NSAIDS. To the contrary, the reference states, "[a] continuing goal is to be able to reduce the dosage of such narcotic analgesics by combining them with non-addicting ingredients while still maintaining a high level of analgesia [i.e., whether they exhibit synergistic effects or not]"). That is, the reference doesn't state, as purported, "[a] continuing goal is to be able to reduce dosage of such narcotic analgesics by combining them with non-addicting ingredients while still maintaining a high level of analgesia [only if a synergistic relationship can be established]"). Consequently, the "principle of operation" only requires a "reduced dosage" of the narcotic while still maintaining a "high level of analgesia" (e.g., see column 2, lines 5-10). That is exactly what T-614 delivers (e.g., see rejection above disclosing superior analgesic potency, as compared to ibuprofen). Thus, a person of ordinary skill in the art would expect to be able to "reduce the dosage" of the narcotic while still maintaining a "high level of analgesia" in accordance with the principle of operation set

forth in the Baker et al. reference. Furthermore, the reference provides examples where a synergistic relationship between narcotic and the analgesic are not even required (e.g., see columns Baker et al., columns 1 and 2, especially column 1 lines 30-37, "no evidence or suggestions of other than an additive analgesic effect for the combination [was established for ibuprofen/codeine]"). In addition, T-614 would also decrease potential side effects such as unwanted gastrointestinal ulcerogenic actions or water/sodium excretions.

In addition, the mere substitution of one analgesic for another does not rise to the level of "substantial" reconstruction or redesign as in cases like *In re Ratti*, 270 F.2d 810, 123 USPQ 349 (CCPA 1959) (Claims were directed to an oil seal comprising a bore engaging portion with outwardly biased resilient spring fingers inserted in a resilient sealing member. The primary reference relied upon in a rejection based on a combination of references disclosed an oil seal wherein the bore engaging portion was reinforced by a cylindrical sheet metal casing. Patentee taught the device required rigidity for operation, whereas the claimed invention required resiliency. The court reversed the rejection holding the "suggested combination of references would require a substantial reconstruction and redesign of the elements shown in [the primary reference] as well as a change in the basic principle under which the [primary reference] construction was designed to operate." 270 F.2d at 813, 123 USPQ at 352.). To the contrary, the courts have held that the mere substitution of one equivalent compound for another to treat the same physiological problem (e.g., T-614 for ibuprofen to treat inflammatory pain) does not represent a "teaching away" or a change in "principle of operation" as purported (e.g., see *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) noted above wherein the court held that it is *prima*

facie obvious to combine two (or more) compositions each of which is taught by the prior art to be useful for the same purpose).

[4] According to *Smithkline* (cited by Applicants), the examiner must "show some teaching or suggestion in the references to support their use in the particular claimed combination." *Smithkline Diagnostics, Inc., v. Helena Labs. Corp.*, 859 F.2d 878, 887, 8 USPQ2d 1468, 1475 (Fed. Cir. 1988). For example, *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529 (Fed. Cir. 1988) instructs at 473, 5 USPQ2d at 1531:

> The consistent criterion for determination of obviousness is whether the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success . . . . Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure.

Here, Tanaka et al. provide ample motivation/expectation for success for making the T-614/ibuprofen substitution (e.g., see Tanaka et al., Summary; wherein Tanaka et al. disclose greater anti-inflammatory potency and fewer side effects for T-614). Thus, Tanaka et al. provide a strong motivating force (e.g., increased potency with decreased side effects) that would impel one skilled in the art to do what applicant are currently claiming (*Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Int. 1993)). In addition, a person of ordinary skill in the art would not have to "pick and choose" from among a wide range of variables to construct the currently claimed invention as purported because Tanka et al. only disclose favorable interactions between T-614 and ibuprofen, which is the preferred embodiment disclosed in the Baker et al. reference.

[5] The Examiner contends that to the extent that Applicants are simply repeating their previous arguments, those issues were adequately addressed in the above sections, which are incorporated in their entireties herein by reference.

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

7. Claim 38, 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baker et al. '937 and Tanaka et al., as applied to claims 38, 47, 48 and 50-52 above, and further in view of Oshlack et al. US Pat. No. 5,472,712 (12/95) or Oshlack et al. US Pat. No. 6,294,195 (9/01: effectively filed 10/93 or earlier).

The substance of the above obviousness rejection is hereby incorporated by reference in its entirety.

Although the Baker reference teaches oral dosage forms that include "sustained release" formulations (e.g. tablets, capsules, etc: see col. 3-4, especially col. 4) utilizing "sustained release carriers", the Baker reference fails to explicitly teach "a sustained release carrier which provides a sustained release of the oxycodone and/or ... salt thereof".

However, the use of sustained release dosage forms for opioid analgesics, including oxycodone which utilize sustained release carriers employing beads which are coated with the opioid drug or which include substrate layers which include the drugs is known in the art to effectuate delayed release of extended duration. E.g. see Oshlack et al. and Oshlack patent references.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time of applicant's invention to utilize sustained release carriers for oxycodone including beads/layers as taught by the Oshlack and Oshlack et al. patents for use in the Baker compositions since Baker specifically teaches using "sustained release formulations" and further in view of the advantages

of utilizing the Oshlack patent sustained release carriers including delayed drug release of extended duration.

Response

8. Applicant's arguments directed to the above 35 U.S.C. § 103(a) rejection were fully considered (and are incorporated in their entirety herein by reference) but were not deemed persuasive for the following reasons. Please note that the above rejection has been modified from it original version to more clearly address applicants' newly amended and/or added claims and/or arguments.

Applicants argue, "Oshlack references do not cure the deficiencies of the Baker reference in view of the Tanaka reference as set forth above" (e.g., see 4/11/06 Response, page 7, section c).

This is not found persuasive for the following reasons:

The Examiner contends that to the extent that Applicants are simply repeating their previous arguments, those issues were adequately addressed in the above sections (which are incorporated in their entireties herein by reference).

Accordingly, the 35 U.S.C. § 103(a) rejection cited above is hereby maintained.

Conclusion

Applicant's amendment necessitated any new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon D. Epperson, Ph.D.
July 31, 2006

JON EPPERSON, PH.D.
PATENT EXAMINER